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POSTER ABSTRACTS

802.CHEMICAL BIOLOGY AND EXPERIMENTAL THERAPEUTICS

Transient CDK9 Inhibition with AZD4573 Effectively Induces Apoptosis in Burkitt Lymphoma As a Monotherapy in Pre-Clinical Models

Danielle S Potter[1], *India Ott*[1], *Jamal Saeh*[2], *Stephen Fawell*[1], *Lisa Drew, PhD*[3], *Justine Roderick-Richardson*[1]

[1] Early Oncology R&D TDE, AstraZeneca, Waltham, MA
[2] Hematology, Oncology R&D, AstraZeneca, Waltham, MA
[3] AstraZeneca, Waltham, MA

Burkitt Lymphoma (BL) accounts for almost two thirds of all B-cell non-Hodgkin lymphoma cases in children and adolescents. It may affect the jaw, bones of the face, bowel, kidney, ovaries and in some cases spread to the central nervous system. Nearly all types of BL are characterized by c-MYC gene translocation of chromosome 8 with immunoglobulin genes at chromosome 2, 14 or 22 resulting in high levels of the transcription factor. Recently, MCL-1 was shown to be overexpressed in BL and is a critical survival factor in pre-clinical BL models using genetic and chemical approaches.

CDK9, a serine/threonine kinase, regulates transcription elongation through phosphorylation of RNA polymerase II at serine 2 (pSer2-RNAPII). AZD4573 is a highly potent and selective CDK9 inhibitor that results in downregulation of short-lived transcripts and labile proteins such as c-MYC and key survival proteins including MCL-1 and BFL-1, resulting in apoptosis in several hematological malignancies (Cidado *et al.* 2020 & Boiko *et al.* 2021)

We selected several preclinical BL models to assess the rapid apoptogenic potential of AZD4573 *in vitro* and *in vivo*. To measure apoptosis, we evaluated cleaved caspase-3 (CC3) induction following acute treatment (6h) using Caspase-Glo 3/7. Using this assay, we found that 3 BL models were sensitive to CDK9 inhibition (EC50 < 100nM; max. CC3 > 50%) and 2 were resistant (EC50 > 100nM; max. CC3 < 50%). Treatment with AZD4573 in these sensitive BL cell line models decreased pSer2-RNAPII, and downregulation of MCL-1 and c-MYC within 6 hours. In AZD4573 resistant lines we observed relatively higher levels of anti-apoptotic proteins BCL2 and BCL-xL, compared to the sensitive cell lines. These increased levels potentially lead to the decreased sensitivity to AZD4573, which does not reduce levels of BCL-2 and BCL-xL due to their longer half-life. Using CRISPR genetic knockouts we demonstrate that BL cell lines are dependent on c-MYC and MCL-1 and that loss of these protein decreases caspase induction after AZD4573 treatment, highlighting the importance of these proteins in driving the efficacy of AZD4573. *In vivo* AZD4573 dosed on a once weekly schedule resulted in tumor growth inhibition in aggressive BL cell line xenografts Namalwa and Ramos (40-60%) and decreased pSer2-RNAPII, MCL-1 and c-MYC and increased CC3 8 hours after treatment. AZD4573 is currently in a phase 2 study (NCT05140382) to assess the efficacy, safety, and PK of AZD4573 in patients with relapsed or refractory Peripheral T-cell lymphomas (pTCL). Our findings demonstrate that targeting CDK9 with AZD4573 can effectively induce apoptosis in pre-clinical BL models and could be an effective therapy for BL patients.

Disclosures Potter: *Astra Zeneca:* Current Employment, Current equity holder in publicly-traded company. **Ott:** *Astra Zeneca:* Current Employment, Current equity holder in publicly-traded company. **Saeh:** *AstraZeneca:* Current Employment, Current equity holder in publicly-traded company. **Fawell:** *Astra Zeneca:* Current Employment, Current equity holder in publicly-traded company. **Drew:** *AstraZeneca:* Current Employment, Current equity holder in publicly-traded company. **Roderick-Richardson:** *AstraZeneca:* Current Employment, Current equity holder in publicly-traded company.

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